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MAJOR ARTICLE

The Burden and Clinical Presentation of Pulmonary Tuberculosis in Adults With Severe Respiratory Illness in a High Human Immunodeficiency Virus Prevalence Setting, 2012–2014

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Background. Understanding the burden and clinical presentation of tuberculosis in patients with severe respiratory illness (SRI) has important implications for anticipating treatment requirements.

Methods. Hospitalized patients aged ≥15 years with SRI at 2 public teaching hospitals in periurban areas in 2 provinces (Edendale Hospital in Pietermaritzburg, KwaZulu-Natal Province and Tshepong Hospital in Klerksdorp, North West Province) were enrolled prospectively from 2012 to 2014. Tuberculosis testing included smear microscopy, culture, or Xpert MTB/Rif.

Results. We enrolled 2486 individuals with SRI. Of these, 2097 (84%) were tested for tuberculosis, 593 (28%) were positive. Tuberculosis detection rate was 18% (133 of 729) in individuals with acute (≤14 days) presentation and 34% (460 of 1368) in those with chronic (>14 days) presentation. Among laboratory-confirmed tuberculosis cases, those with acute presentation were less likely to present with cough (88% [117 of 133] vs 97% [447 of 460]; ajusted odds ratio [aOR] = 0.2, 95% confidence interval [CI] = 0.1–0.5), night sweats (57% [75 of 132] vs 73% [337 of 459]; aOR = 0.4, 95% CI = 0.3–0.7), or be started on tuberculosis treatment on admission (63% [78 of 124] vs 81% [344 of 423]; aOR = 0.4, 95% CI = 0.3–0.7), but they were more likely to be coinfected with pneumococcus (13% [16 of 124] vs 6% [26 of 411]; aOR 2.3, 95% CI 1.3–5.3) than patients with chronic presentation. Annual incidence of acute and chronic tuberculosis-associated SRI per 100 000 population was 28 (95% CI = 22–39) and 116 (95% CI = 104–128), respectively.

Conclusions. In this setting, tuberculosis, including acute presentation, is common in patients hospitalized with SRI.

Keywords. HIV; severe respiratory illness; South Africa; tuberculosis.

Tuberculosis is an important cause of severe respiratory illness (SRI) causing significant morbidity and mortality globally. In 2015, an estimated 10.4 million people developed tuberculosis and 1.8 million died from the disease, 0.4 million (22%) of whom were infected with human immunodeficiency virus (HIV) [1]. In South Africa in the same year, there were an estimated 454 000 incident cases of tuberculosis and 258 000 (57%) were infected with HIV [1].

The 2014, South African national guidelines for tuberculosis management recognized the importance of early diagnosis and treatment of tuberculosis and advocated that sputa be tested in patients with symptoms of tuberculosis, especially those who are infected with HIV irrespective of the duration of cough. However, for HIV-uninfected patients, these guidelines advise testing only patients with chronic duration of symptoms (ie, cough or fever >14 days) [2]. The World Health Organization (WHO) guidelines also call for intensified case finding among HIV-infected individuals and recommend screening for tuberculosis in patients with any current symptoms of tuberculosis [3]. In an earlier publication including data from the same hospitals as the current study, we found that only 38% of individuals admitted for lower respiratory tract infection (LRTI) with any symptom duration were tested for tuberculosis, whereas 80% of admitted patients ≥15 years with LRTI were infected

Received 21 December 2016; editorial decision 25 May 2017; accepted 5 June 2017.

Presented in part: National Institute for Communicable Disease GERMS Annual Surveillance Review on the 13–14 October 2015, NICD, Johannesburg.

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DOI: 10.1093/ofid/ofx116

with HIV [4]. In addition, clinicians were significantly less likely to test patients with acute symptoms for tuberculosis and to start them on tuberculosis treatment [4]. Understanding the spectrum of clinical presentation of tuberculosis may contribute to timely diagnosis and treatment and subsequent better control of the tuberculosis epidemic. Among HIV-infected and -uninfected persons aged ≥15 years hospitalized with SRI in South Africa during 2012–2014, we aimed to describe the following: (1) factors associated with acute compared with chronic presentation of SRI irrespective of laboratory diagnosis; (2) the incidence of laboratory-confirmed acute and chronic presentation of pulmonary tuberculosis; (3) factors associated with laboratory-confirmed pulmonary tuberculosis among patients tested for tuberculosis; and (4) factors associated with acute and chronic presentation among patients with laboratory-confirmed tuberculosis.

METHODS

Study Design

This study used data collected as part of surveillance for SRI [5]. Prospective hospital-based active surveillance was conducted for SRI at 2 sentinel surveillance sites (Edendale Hospital in Pietermaritzburg, Umgungundlovu District, KwaZulu-Natal Province and Tshepong Hospital in Klerksdorp, Matlosana District, North West Province) from July 2012 to August 2014.

Case Definitions

A case of SRI was defined as admission with a physician diagnosis of LRTI (eg, pneumonia, bronchiolitis, bronchitis, and pleural effusion, suspected or confirmed tuberculosis) irrespective of symptom duration and included individuals who met the WHO severe acute respiratory illness (SARI) case definition of cough and fever presenting within 10 days of onset of illness [6].

Study Procedures

Patients admitted from Sunday at 5:00 PM through to 1:00 PM on Fridays were screened for inclusion. Patients who refused or were unable to give consent and patients from outside the catchment area of the respective hospitals were excluded. Data on clinical presentation, previous medical history, antiviral therapy for HIV-infected individuals, inpatient investigations, and management and outcome were collected by interview and medical record review. Patients were followed-up until discharge. Treatment decisions, including initiation of tuberculosis treatment based on laboratory confirmation or empirically, and diagnostic tests were performed according to the attending physician.

In addition, combined nasopharyngeal (NP) and oropharyngeal (OP) swabs, expectorated or induced sputum, and blood specimens were collected from consenting patients. We instituted testing for tuberculosis for all consenting patients, and details of testing for tuberculosis are included in the Supplementary Material.

Laboratory Methods

Nasopharyngeal and OP swabs were transported in universal transport medium at 4–8°C to the National Institute for Communicable Diseases (NICD) within 72 hours of collection. Combined NP and OP swabs were tested for influenza A and B and 8 other respiratory viruses (parainfluenza virus types 1, 2, and 3; respiratory syncytial virus; adenovirus; rhinovirus; human metapneumovirus; and enterovirus) by real-time, reverse-transcription polymerase chain reaction (PCR) [7]. Sputum samples were frozen at −20°C and shipped on dry ice weekly to NICD. Testing for tuberculosis at the hospital laboratory was performed by smear microscopy, culture, and/or XpertMTB/Rif based on the hospital testing algorithm. At NICD, in 2012 testing only included culture and microscopy was added in 2013. Details of tuberculosis testing are included in Supplementary Material. Determination of HIV status is described in detail in Supplementary Material. In brief, HIV testing was not required for participation, and HIV results were obtained from clinical records when available. For consenting patients with unavailable results, either bedside testing was done or a dried blood spot was tested as part of surveillance. Testing included HIV enzyme-linked immunosorbent assay (ELISA) for patients aged ≥18 months and PCR for children aged <18 months if the ELISA was reactive.

Tuberculosis Status

Tuberculosis status was determined using tuberculosis results from specimens tested at the site laboratory and at NICD. A laboratory-confirmed tuberculosis case was defined as an individual with any positive result for acid-fast bacilli on microscopy, *Mycobacterium tuberculosis* on culture, or PCR (Xpert MTB/Rif or MTBDRplus) from the current hospital admission.

Symptom Duration

For duration of symptoms, we used the date of onset of symptoms as reported by the patient and considered cough and fever as the main variables to categorize duration of symptoms as either an acute (≤14 days) or chronic (>14 days) presentation. The cutoff of 14 days was chosen a priori based on South African guidelines for tuberculosis screening for HIV-negative individuals.

Incidence Calculation

Incidence estimates of acute and chronic tuberculosis-associated SRI hospitalization (per 100 000 population) for Pietermaritzburg and Klerksdorp were calculated for 2013. Population denominators for the hospital catchment population were accessed from the 2011 census data as collected by Statistics South Africa [8]. Mid-year population figures by age group were estimated for the districts served by the hospitals. These population numbers were adjusted for proportions of people in the hospital catchment area that attended the surveillance hospital for care for respiratory illness using information from healthcare utilization surveys previously conducted at

each site (Karen Wong and Jo McAnerney, Oral communication, May 2016). Data on all admissions during 2013, including nonenrolled individuals, were collected and used to estimate the number of SRI cases missed during the study period due to nonenrollment over weekends and refusal. The incidence of acute and chronic tuberculosis-associated SRI hospitalizations/100 000 population for 2013 was estimated using the number of patients with acute and chronic presentation testing positive for tuberculosis, adjusting for nonenrollment (due to refusal and over weekend admissions) and patients who did not seek care by age groups divided by the mid-year population estimates for 2013 and multiplied by 100 000. Confidence intervals (CIs) were calculated using the Poisson distribution.

Data Analysis

To identify factors associated with tuberculosis positivity and acute compared with chronic presentation of tuberculosis, we included potential determinants for, as well as outcomes or characteristics of, the primary endpoints of the analysis. We implemented 3 multivariable logistic regression models to identify factors associated with the following: (1) acute compared with chronic presentation among patients hospitalized with SRI irrespective of laboratory diagnosis; (2) laboratory confirmation of tuberculosis among patients admitted with SRI with symptoms of any duration and with available tuberculosis results; and (3) acute compared with chronic presentation among individuals with laboratory-confirmed tuberculosis to assess whether cases with an acute presentation differed in presentation and outcome because they would likely not have been tested for tuberculosis especially if they were HIV negative. We repeated model (3) among HIV-infected and HIV-uninfected individuals separately.

For the multivariate model, all factors significant at $P < .1$ on univariate analysis were evaluated, and nonsignificant factors at $P < .05$ were then dropped from the multivariable model using stepwise forward selection. All 2-way interactions in the final multivariable additive model were evaluated. Two-sided P values <.05 were considered significant throughout. Stata version 13.1 (StataCorp Limited, College Station, TX) was used for the analysis.

RESULTS

From July 2012 through August 2014, 4045 patients fulfilling the SRI case definition were enrolled; 2486 (61%) were aged ≥15 years and were included in the analysis. Of these, 866 (35%) had an acute presentation. A total of 2097 of 2486 (84%) patients were tested for tuberculosis, with equal proportions tested among those with an acute (84%; 729 of 866) and chronic (84%; 1368 of 1620) presentation (Figure 1). Tuberculosis was detected in 28% (593 of 2097) of enrolled individuals, 18% (133 of 729) and 34% (460 of 1368) in those with an acute and chronic presentation, respectively ($P < .001$). Results of different tuberculosis microbiologic tests are included in the Supplementary Material.

Compared with patients tested for tuberculosis, controlling for hospital, patients not tested were less likely to present with cough (ajusted odds ratio [aOR], 0.3; 95% CI, 0.2–0.5) or night

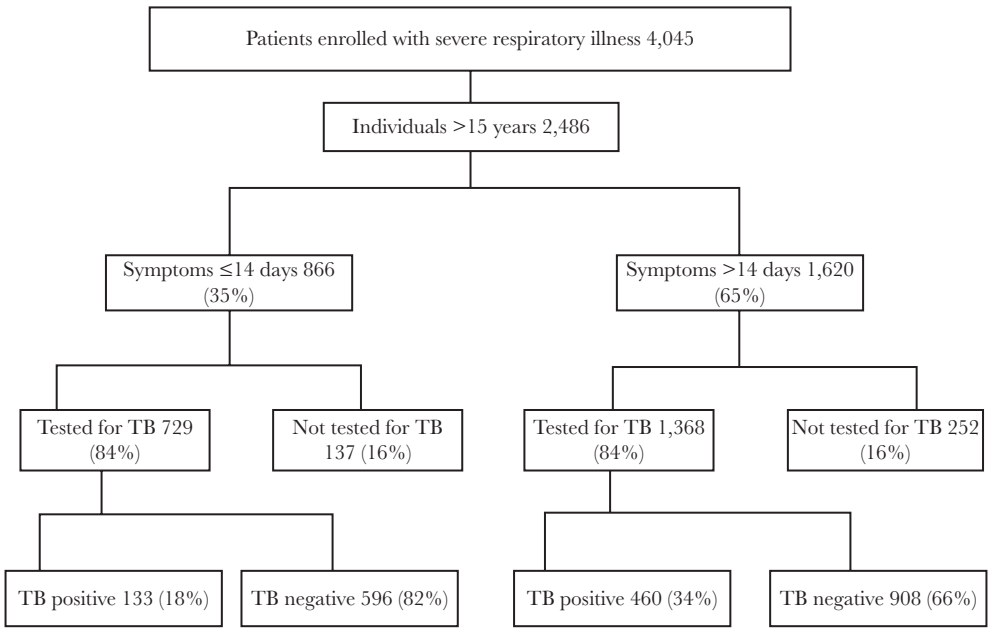

Figure 1. Individuals admitted with severe respiratory illness and consented for enrollment by symptom duration and laboratory-confirmed tuberculosis (TB) status, South Africa, July 2012–August 2014.NOTE: Reasons for not testing for TB ($n = 389$): 54% (210) not able to expectorate and sputum induction contraindicated or too sick or weak to cough up induced sputum, 30% ($n = 117$) induction not successful, 6% ($n = 23$) refused, 10% ($n = 39$) reason not recorded.

sweats (aOR, 0.7; 95% CI, 0.6–0.9) but were more likely to be admitted for >7 days compared with <3 days (aOR, 1.7; 95% CI, 1.1–2.4) and to die (aOR, 3.1; 95% CI, 2.3–4.1) (Supplementary Table 1). There was no significant difference in HIV status among patients tested (77% [1438 of 1877]) and not tested (72% [247 of 344]) for tuberculosis ($P = .06$).

The overall HIV prevalence in patients with SRI was 76% (1685 of 2221) and varied by age group: 72% (134 of 186) in those 15–24 years, 91% (1071 of 1179) in those 25–44 years, 66% (437 of 665) in those 45–64 years, and 23% (43 of 191) in those ≥65 years ($P < .001$). Human immunodeficiency virus status also varied by tuberculosis disease: 75% (1014 of 1355) and 81% (424 of 522) in tuberculosis-uninfected and -infected individuals, respectively ($P = .003$). Of the 1685 HIV-infected SRI patients, 389 (23%) were diagnosed with HIV at the current admission. Of 1482 HIV-infected SRI patients with information on HIV treatment, 45% (674) were receiving HIV treatment at time of admission.

Comparison of Characteristics of Individuals With Acute Presentation to Individuals With Chronic Presentation Hospitalized With Severe Respiratory Illness

Of the patients with acute presentation, 95% (820 of 866) had symptom duration ≤10 days, and 28% (231 of 820) of these met the WHO SARI case definition of LRTI with reported or documented fever, cough, and symptoms ≤10 days [6]. On multivariable analysis, compared with patients with a chronic presentation, patients with an acute presentation were less likely to present with cough or night sweats, to have laboratory-confirmed tuberculosis, to be started on treatment for tuberculosis on current admission, to be hospitalized for a longer duration ≥3 days, and to die (Table 1). The HIV prevalence was similar (73% [568 of 773] vs 77% [1117 of 1448]) in patients with acute and chronic presentation, respectively.

Factors Associated With Laboratory Confirmation of Tuberculosis Among Patients Admitted With Severe Respiratory Illness of Any Duration and Tested for Tuberculosis

Among 2097 patients with available tuberculosis results, 28% (593 of 2097) tested positive for tuberculosis at the current admission. Eighteen percent (33 of 183) of those who met the WHO SARI case definition tested positive for tuberculosis.

On multivariable analysis, compared with tuberculosis-negative patients, patients with laboratory-confirmed tuberculosis of any symptom duration were less likely to be in older age groups >45 year compared with the 15–24 age group, to be coinfected with pneumococcus, and to have received oxygen therapy. They were more likely to present with symptoms >14 days (Table 2). The prevalence of influenza (4% vs 6%, $P = .09$) was similar in patients with and without tuberculosis disease of any duration.

Factors Associated With Acute Presentation Compared to Chronic Presentation in Cases With Laboratory-Confirmed Tuberculosis

Of the 593 laboratory-confirmed tuberculosis cases, 22% (133) and 78% (460) had an acute and chronic presentation, respectively. Human immunodeficiency virus prevalence among laboratory-confirmed cases was 81% (424 of 522), and it was similar in those with acute (83%, 102 of 123) and chronic (81%, 322 of 399) presentation ($P = .51$). Among HIV-uninfected laboratory-confirmed cases, 21% (21 of 98) had an acute presentation. On multivariable analysis, among patients with laboratory-confirmed tuberculosis, cases with acute presentation were less likely to present with cough (aOR, 0.2; 95% CI, 0.1–0.5) or night sweats (aOR, 0.4; 95% CI, 0.3–0.7) or be started on treatment for tuberculosis at current admission (aOR, 0.4; 95% CI, 0.3–0.7) than cases with chronic presentation. In contrast, they were more likely to have pneumococcal coinfection (aOR, 2.6; 95% CI, 1.3–5.3). The case-fatality ratio was not statistically different between laboratory-confirmed tuberculosis patients with acute (8%, 11 of 131) and chronic (13%, 56 of 447) presentation ($P = .194$) (Table 3). Similar results were seen when restricting analysis to HIV-infected patients with laboratory-confirmed tuberculosis (Supplementary Material).

Incidence of Hospitalization for Tuberculosis-Associated Severe Respiratory Illness

The estimated overall incidence (per 100 000 population) of hospitalization for tuberculosis-associated SRI was 144 (95% CI, 131–158), ranged from 43 to 200 per 100 000 among age groups, and was significantly higher in Klerksdorp than in Pietermaritzburg (181 [95% CI, 162–201] vs 93 [95% CI, 77–111]). The annual incidence of tuberculosis-associated SRI in individuals hospitalized with acute presentation was 28 per 100 000 population (95% CI, 22–39), increased with increasing age, and was highest in individuals ≥65 years (94 cases per 100 000 population; 95% CI, 54–153). The incidence of tuberculosis-associated SRI in individuals with chronic presentation was 116 per 100 000 population per annum (95% CI, 104–128) and was highest in individuals aged 25–44 years (145 cases per 100 000 population; 95% CI, 125–166) (Figure 2). The incidence of tuberculosis-associated SRI was lower in individuals with acute compared with chronic presentation, except in individuals aged ≥65 years where there was no significant difference (0.8; 95% CI, 0.4–1.8) (Figure 2).

DISCUSSION

We found that in our setting, a high proportion of adolescents and adults admitted with SRI regardless of symptom duration had active tuberculosis. For patients with acute presentation, 1 in 5 (18%) were found to have active tuberculosis, whereas among those with longer duration of symptoms, 1 in 3 (34%) had active tuberculosis. Although the likelihood of tuberculosis disease was higher if symptom duration was >14 days, additional numbers of cases will be identified if laboratory testing for tuberculosis is conducted for adults with SRI irrespective of symptom duration or HIV status. In particular, 21% of HIV-uninfected patients with laboratory-confirmed tuberculosis had an acute presentation, and these would have been missed by the South African tuberculosis testing guidelines [2]. Although the HIV-uninfected tuberculosis

Table 1. Demographic and Clinical Characteristics of Individuals ≥15 Years Admitted With Severe Respiratory Illness by Symptom Duration (≤ or >14 days), in South Africa, July 2012–August 2014 (*N* = 2486)

Variables	Acute Presentation (≤14 Days) n/N (%)	Chronic Presentation (>14 Days) n/N (%)	Univariate Analysis (Acute Compared With Chronic Presentation)		Multivariable Analysis (Acute Compared With Chronic Presentation)	
			OR (95% CI)	P Value	OR (95% CI)	P Value
Age						
15–24	69/866 (8)	137/1620 (8)	Reference		Reference	
25–44	459/866 (53)	860/1620 (53)	1.1 (0.8–1.4)	.715	1.3 (0.8–2.0)	.221
45–64	244/866 (28)	500/1620 (31)	1.0 (0.7–1.3)	.850	1.2 (0.7–1.9)	.514
65+	94/866 (11)	123/1620 (8)	1.5 (1.1–2.3)	**.038**	1.1 (0.6–2.0)	.721
Female sex	508/866 (57)	816/1619 (50)	1.4 (1.2–1.6)	**<.001**	1.3 (1.0–1.6)	**.027**
Tshepong Hospital	547/866 (63)	1069/1620 (66)	0.9 (0.7–1.1)	.160		
History of cough	748/865 (84)	1564/1620 (96)	0.2 (0.1–0.3)	**<.001**	0.2 (0.1–0.4)	**<.001**
History of fever	374/861 (43)	551/1608 (34)	1.5 (1.2–1.7)	**<.001**	1.4 (1.1–1.8)	**.004**
Night sweats	444/864 (54)	1111/1619 (67)	0.5 (0.4 -0.6)	**<.001**	0.5 (0.4–0.6)	**<.001**
Underlying medical conditions[a]	88/866 (10)	134/1619 (8)	1.3 (0.9–1.7)	.117		
Diabetes	40/865 (5)	37/1619 (2)	2.1 (1.3–3.3)	**.002**	2.1 (1.1–3.8)	**.028**
Mine exposure[c]	83/857 (10)	189/1594 (12)	0.8 (0.6–1.0)	.103		
History of smoking[b]	169/856 (20)	273/1602 (17)	1.2 (1.0–1.5)	.097		
History of alcohol[b]	214/858 (25)	349/1603 (22)	1.2 (1–1.5)	.075		
Tested for TB	729/866 (84)	1368/1620 (84)	1.0 (0.8–1.2)	.863		
Laboratory confirmed TB[g]	133/729 (18)	460/1368 (34)	0.4 (0.3–0.5)	**<.001**	0.7 (0.5–0.9)	**.004**
History of TB treatment[e]	73/863 (8)	189/1612 (12)	0.7 (0.5–0.9)	**.012**		
HIV infected	568/773 (73)	1117/1448 (77)	0.8 (0.7–1.0)	**.055**		
Influenza-positive	59/842 (7)	72/1587 (4)	0.6 (0.4–0.9)	**.011**		
Pneumococcal coinfection[d]	144/790 (18)	144/1457 (10)	2.0 (1.6–2.6)	**<.001**	1.9 (1.5–2.6)	**<.001**
Viral coinfection	231/842 (27)	429/1587 (27)	1.0 (0.8–1.2)	.832		
Required oxygen	300/836 (36)	569/1570(36)	1.0 (0.8–1.2)	.862		
Antibiotics on admission	823/850 (97)	1509/1591 (95)	1.7 (1.1–2.6)	**.026**		
Started on TB treatment[f]	247/803 (31)	809/1457 (56)	0.3 (0.3–0.4)	**<.001**	0.4 (0.3–0.6)	**<.001**
Duration of hospitalization						
<3 days	168/788 (21)	226/1484 (15)	Reference		Reference	
3–7 days	337/788 (43)	605/1484 (41)	0.7 (0.6–0.9)	**.018**	0.7 (0.5–0.9)	**.013**
8+ days	283/788 (34)	653/1484 (44)	0.6 (0.5–0.7)	**<.001**	0.6 (0.4–0.8)	**.001**
Died during admission	91/824 (11)	228/1546 (15)	0.7 (0.5–0.9)	**.012**	0.7 (0.5–0.97)	**.038**

Bold indicates significant variables.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PCR, polymerase chain reaction; TB, tuberculosis.

[a]Underlying conditions included any of the following: asthma, other chronic lung disease, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), immunocompromising conditions excluding HIV infection (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions), or pregnancy. Comorbidities were considered absent in cases for which the medical records stated that the patient had no underlying medical condition or when there was no direct reference to that condition.

[b]Current history.

[c]Any history of having worked in the mine.

[d]*lytA* PCR positive for *Streptococcus pneumoniae* on blood specimen.

[e]History of TB treatment within the last 12 months of current admission.

[f]Started on TB treatment at current admission; excludes those already on TB treatment at time of admission (*n* = 144). Of the 1056 patients started on TB treatment, 42% (441 of 1056) had a negative TB result, 36% (376 of 1056) tested positive, and 23% (239 of 1056) had missing/pending results at the time of initiation of TB treatment.

[g]6% (38/593) only detected on culture.

cases with acute presentation constituted 3.5% of all tuberculosis cases in this study, in a setting with high tuberculosis prevalence and where tuberculosis is the leading cause of death, any opportunity to diagnose tuberculosis should be used. Studies have reported a high prevalence or incidence of active tuberculosis in South African communities including in cases where tuberculosis was not suspected [9–11]. In a postmortem study conducted in a community served by one of the hospitals included in our study, 31% of patients who died at home with uncategorized cause of death had tuberculosis [10]. Wong et al [11] reported that among HIV-positive individuals, ~30% of microbiologically and histologically proven tuberculosis infections on postmortem were clinically not suspected at the time of death.

In our study, 59% and 27% of laboratory-confirmed tuberculosis cases did not present with fever and chronic cough, respectively, potentially reducing the clinician's suspicion of tuberculosis even further. The atypical clinical presentation of tuberculosis in our study is likely to be related to HIV infection

Table 2. Demographic and Clinical Characteristics Associated With Laboratory-Confirmed Tuberculosis Among Cases Admitted With Severe Respiratory Illness of Any Duration and Tested for Tuberculosis at Two Sites in South Africa, 2012–2014 (*N* = 2097)

Variables	Tuberculosis Negative n/N (%)	Tuberculosis Positive n/N (%)	Univariate Analysis		Multivariable Analysis	
			OR (95% CI)	P Value	OR (95% CI)	P Value
Age						
15–24	107/1504 (7)	63/593 (11)	Reference		Reference	
25–44	780/1504 (52)	365/593 (62)	0.8 (0.6–1.1)	.179	0.7 (0.5–1.1)	.114
45–64	475/1504 (32)	144/593 (24)	0.5 (0.4–0.7)	**<.001**	0.6 (0.4–0.9)	**.007**
65+	142/1504 (9)	21/593 (3)	0.3 (0.1–0.4)	**<.001**	0.3 (0.1–0.5)	**<.001**
Female gender	801/1503 (53)	397/593 (51)	0.9 (0.7–1.1)	.295		
Klerksdorp Tshepong	991/1504 (66)	397/593 (67)	1.04 (0.9–1.3)	.645		
Duration of symptoms >14 days	908/1504 (60)	460/593 (76)	2.3 (1.8–2.8)	**<.001**	1.6 (1.2–2.0)	**.001**
History of cough (any duration)	1416/1503 (94)	564/593 (95)	1.2 (0.8–1.8)	.419		
Chronic cough >14 days	833/1503 (55)	833/592 (73)	2.2 (1.8–2.7)	**<.001**		
History of fever	544/1493 (37)	239/590 (41)	1.2 (0.9–1.4)	.084		
Night sweats	927/1503 (62)	412/591 (70)	1.4 (1.2–1.8)	**<.001**		
Underlying medical condition[a]	161/1503 (11)	27/593 (5)	0.4 (0.3–0.6)	**<.001**		
Diabetes	48/1502 (3)	12/593 (2)	0.6 (0.3–1.2)	.151		
History of TB treatment[e]	142/1499 (9)	68/589 (28)	1.2 (0.9–1.7)	.157		
HIV infected	1014/1355 (75)	424/522 (81)	1.5 (1.1–1.9)	**.003**		
Worked in mine[c]	173/1484 (12)	68/583 (12)	1.0 (0.7–1.3)	.997		
History of smoking[b]	281/1488 (19)	113/586 (19)	1.0 (0.8–1.3)	.835		
History of alcohol[b]	374/1489 (25)	128/586 (22)	0.8 (0.6–1.0)	.117		
Influenza-positive	89/1471 (6)	24/582 (4)	0.7 (0.4–1.06)	.086		
Pneumococcal coinfection[d]	212/1366 (16)	42/535 (8)	0.5 (0.3–0.7)	**<.001**	0.6 (0.4–0.9)	**.024**
Viral coinfection	419/1471 (28)	169/582 (29)	1.03 (0.8–1.3)	.802		
Invasive bacterial infection on culture[g]	7/251 (3)	2/122 (2)	0.6 (0.1–2.8)	.502		
Required oxygen	547/1445 (38)	171/584(29)	0.7 (0.5–0.8)	**<.001**	0.7 (0.6–0.9)	**.005**
Antibiotics on admission	1421/1468 (97)	554/588 (94)	0.5 (0.3–0.8)	**.007**		
TB treatment started[f]	470/1371 (34)	422/547 (77)	6.5 (5.1–8.1)	**<.001**	5.6 (4.-7.2)	**<.001**
Duration of hospitalization						
<3 days	247/1364 (18)	102/554 (18)	Reference			
3–7 days	557/1364 (41)	248/554 (45)	1.1 (0.8–1.4)	.592		
8+ days	560/1364 (41)	204/554 (37)	0.9 (0.7–1.2)	.382		
Died during admission	152/1423 (11)	67/578 (12)	1.1 (0.8–1.5)	.555		

Bold indicates significant variables.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PCR, polymerase chain reaction; TB, tuberculosis.

[a]Underlying conditions included any of the following: asthma, other chronic lung disease, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), immunocompromising conditions excluding HIV infection (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions), or pregnancy. Comorbidities were considered absent in cases for which the medical records stated that the patient had no underlying medical condition or when there was no direct reference to that condition.

[b]Current history.

[c]Any history of having worked in the mine.

[d]*lytA* PCR positive for *Streptococcus pneumoniae* on blood specimen.

[e]History of TB treatment within the last 12 months of current admission.

[f]Started on TB treatment at current admission; excludes those already on TB treatment at time of admission (*n* = 108).

[g]Invasive isolates were defined as a bacterial pathogen isolated from blood or pleural fluid from a specimen taken within 48 hours of hospitalization; organisms viewed as likely contaminants were excluded. Two percent (9 of 373) of patients had a positive blood culture (5 *S pneumoniae*, 2 *Staphylococcus aureus*, and 1 *Escherischia coli*). Two percent (2 of 122) of laboratory-confirmed TB patients had a positive blood culture (1 *E coli* and 1 *S aureus*).

because 81% of patients in our study were infected with HIV. Symptom screening has been reported to perform poorly in HIV-infected patients, particularly in those on antiretroviral therapy [12, 13]. Early detection and prompt treatment are key to the success of tuberculosis infection control [14]. To facilitate diagnosis, minimize delays to treatment initiation, interrupt transmission, and improve patient outcomes, studies have advocated for rapid microbiological diagnosis of tuberculosis, which could be achieved through using rapid diagnostic tests including Xpert and urine assay for lipoarabinomannan (LAM) [15–20]. Urine LAM tests, although not currently part of standard of care in our setting, have been shown to be beneficial especially among HIV-infected individuals with advanced disease where systematic screening of admitted individuals is advised [16–19, 21].

Tuberculosis patients with acute presentation compared with chronic presentation were less likely to present with typical

Table 3. Demographic and Clinical Factors Associated With Acute (≤14 Days) vs Chronic (>14 Days) Presentation Among Individuals ≥15 Years With Laboratory-Confirmed Tuberculosis, July 2012–August 2014 (*N* = 593)

Variables	Acute Presentation n/N (%)	Chronic Presentation n/N (%)	Univariate Analysis		Multivariable Analysis	
			OR (95% CI)	P Value	OR (95% CI)	P Value
Age						
15–24	11/133 (8)	52/460 (11)	Reference		Reference	
25–44	82/133 (62)	283/460 (62)	1.4 (0.7–2.7)	.375		
45–64	33/133 (24)	111/460 (24)	1.4 (0.7–2.9)	.379		
65+	7/133 (5)	14/460 (3)	2.4 (0.8–7.2)	.131		
Female gender	73/133 (55)	228/460 (50)	1.2 (0.8–1.8)	.280		
Tshepong Hospital	89/133 (67)	308/460 (67)	1.0 (0.7–1.5)	.993		
History of any cough	117/133 (88)	447/460 (97)	0.2 (0.1–0.5)	**<.001**	0.2 (0.1–0.5)	**<.001**
History of fever	60/133 (45)	179/457 (41)	1.3 (0.9–1.9)	.220		
Night sweats	75/132 (57)	337/459 (73)	0.5 (0.3–0.7)	**<.001**	0.4 (0.3–0.7)	**<.001**
Underlying medical condition[a]	6/133 (5)	21/460 (5)	0.98 (0.4–2.5)	.979		
History of TB treatment[c]	51/4457(11)	17/132 (13)	1.2 (0.7–2.1)	.586		
Diabetes	5/433 (5)	7/460 (2)	2.5 (0.8–8.1)	.118		
HIV infected	102/123 (83)	322/399 (81)	1.2 (0.7–1.9)	.581		
Influenza positive	9/130 (7)	15/452 (3)	2.2 (0.9–5.1)	.075		
Pneumococcal coinfection[b]	16/124 (13)	26/411 (6)	2.2 (1.1–4.2)	**.019**	2.6 (1.3–5.3)	**.008**
Viral coinfection	40/130 (31)	129/452 (29)	1.1 (0.7–1.7)	.622		
Required oxygen	48/131 (37)	123/453 (27)	1.6 (1.1–2.3)	**.036**		
Started on antibiotics	125/131 (95)	429/457 (94)	1.4 (0.6–3.4)	.505		
Started on TB treatment[d]	78/124 (63)	344/423 (81)	0.4 (0.3–0.6)	**<.001**	0.4 (0.3–0.7)	**.001**
Duration of hospitalization						
<3	21/124 (21)	89/430 (19)	Reference			
3–7	54/124 (42)	194/430 (45)	1.1 (0.6–1.9)	.806		
8+	49/124 (37)	155/430 (36)	1.2 (0.7–2.2)	.501		
Died during admission	11/131 (8)	56/447 (13)	0.6 (0.3–1.3)	.197		

Bold indicates significant variables.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PCR, polymerase chain reaction; TB, tuberculosis.

[a]Underlying conditions included any of the following: Asthma, other chronic lung disease, chronic heart disease (valvular heart disease, coronary artery disease, or heart failure excluding hypertension), liver disease (cirrhosis or liver failure), renal disease (nephrotic syndrome, chronic renal failure), immunocompromising conditions excluding HIV infection (organ transplant, immunosuppressive therapy, immunoglobulin deficiency, malignancy), neurological disease (cerebrovascular accident, spinal cord injury, seizures, neuromuscular conditions) or pregnancy. Comorbidities were considered absent in cases for which the medical records stated that the patient had no underlying medical condition or when there was no direct reference to that condition.

[b]*lytA* PCR positive for *Streptococcus pneumoniae* on blood specimen.

[c]History of TB treatment within the last 12 months of current admission.

[d]Started on TB treatment at current admission; excludes those already on TB treatment at time of admission (*n* = 39).

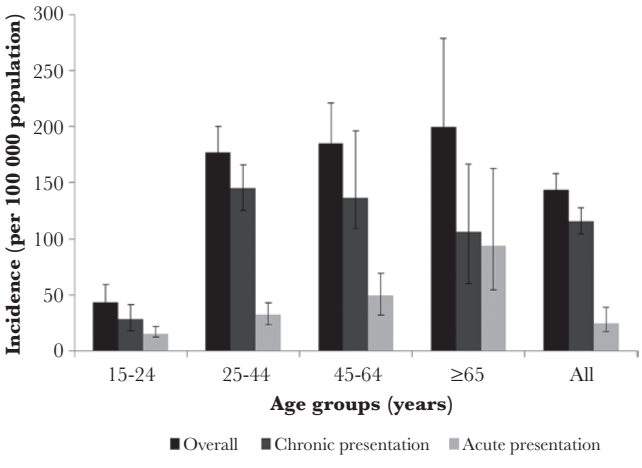

Figure 2. Incidence of tuberculosis-associated severe respiratory illness in acute (≤14 days) vs chronic (>14 days) presentation per 100 000 population, South Africa 2013.

symptoms of tuberculosis such as night sweats and cough and were less likely to be started on tuberculosis treatment by the attending clinician. The delay in initiating tuberculosis treatment, especially among patients with acute presentation, may reflect the clinicians' level of suspicion for tuberculosis in this group of patients. Patients with undiagnosed tuberculosis may continue to spread tuberculosis to other patients and healthcare workers [22–24]. Healthcare service delays have been cited as major contributors to total delay to initiation of tuberculosis treatment [25–27]. A postmortem study in patients dying in hospital found that among patients not suspected of having tuberculosis at the time of death, 42% (40 of 96) were culture positive for tuberculosis and that pneumonia was the leading admission diagnosis (25%) in those not suspected of tuberculosis [28]. This study supports the importance of maintaining a high clinical index of suspicion for tuberculosis in patients presenting with acute SRI symptoms in high HIV and tuberculosis burden settings.

Coinfection with respiratory viruses was common (29%) among tuberculosis-confirmed cases. Four percent were coinfected with influenza: 7% and 3% in patients with an acute and chronic presentation, respectively. This may be an important group to target for influenza vaccination because increased risk of influenza-associated mortality in patients with tuberculosis has been reported [4, 29–31]. Pneumococcal coinfection was identified in 8% of tuberculosis cases and more commonly identified in tuberculosis cases with an acute than chronic presentation. Among cases with an acute presentation, pneumococcus was the most commonly detected copathogen. Studies have postulated an interaction between tuberculosis and pneumococcus [32–36]. This may suggest severe comorbidity as the reason for admission to hospital in patients with tuberculosis. Blood cultures were performed in <20% of enrolled patients with tuberculosis results, which limited our ability to comment on the proportion with bacteremic pneumonia.

The overall incidence of hospitalized tuberculosis-associated SRI was high (144; 95% CI, 131–158), and it was twice as high in the Matlosana district compared with areas around Pietermaritzburg (181 [95% CI, 162–201] vs 93 [95% CI, 77–111]). Because gold mining is a major industry in Klerksdorp, tuberculosis incidence may be higher compared with Pietermaritzburg, which is a nonmining town. Silicosis is a frequent occurrence among miners, and gold miners are at higher risk for acquiring tuberculosis [37]. In addition, mining areas could fuel transmission among general population. Both Matlosana and UMgungundlovu Districts are high HIV-prevalence areas, and SRI cases at Tshepong and Edendale hospital had a similar high HIV prevalence. Additional results on incidence are discussed in the Supplementary Material.

Our study has a number of limitations. This study included hospitalized individuals only and may not be reflective of patients with respiratory symptoms treated in outpatient facilities. Although our study aimed to test all patients admitted with SRI for tuberculosis, only 84% of patients were tested. Tested patients were less likely to die, and were more likely to die, and this could have biased our study. More than half (54%) of patients that were not tested were not able to expectorate and induced sputum was contraindicated or they were either too sick or weak to cough up sputum. In addition, 18% of patients in our study were tested on tuberculosis PCR only and 6% were tested on smear only. It is possible that patients diagnosed as not having tuberculosis did actually have tuberculosis because the sensitivity of diagnostic tests is <100%. Guidelines for testing with the Xpert MTB/Rif advise that a second sample be tested with microscopy and culture especially in HIV-infected patients who test negative for tuberculosis on PCR. For tuberculosis testing at site, we included testing conducted as part of clinical care, and additional testing was conducted as part of surveillance. Surveillance testing initiated in July 2012 used the same systems as clinician-initiated testing and coincided with a campaign to encourage clinician testing because we wanted to make sure that all results would be available to clinicians. For this reason we were not able to tell whether the proportion of clinician-initiated testing for individual cases differed between patients with acute and chronic presentation. In a previous study that included the same sites from 2010 to 2011 when no systematic testing was implemented, we found that testing for tuberculosis was less common in individuals with a duration of symptoms <7 days [4].

Data on cryptococcosis was not collected as part of the main study; therefore, we were not able to assess its contribution. For mortality, we used in-hospital outcome, and the 12% case-fatality ratio reported in our study would likely be higher if patients were followed up after discharge from hospital. According to death notification forms in South Africa, of the 458 933 tuberculosis deaths that occurred in 2013, 106 554 (23%) occurred at home [38]. For incidence calculation, uncertainty may have been introduced through adjustment for nonenrollment, and this was not included in the estimation of CIs. Finally, we only included patients aged ≥15 years in our study and therefore cannot comment on acute and chronic presentation of tuberculosis in children.

CONCLUSIONS

Tuberculosis should be considered in a differential diagnosis of patients presenting with SRI irrespective of the duration of symptoms in high HIV and tuberculosis burden settings such as South Africa. The absence of classic tuberculosis symptoms and an acute presentation should not preclude the possibility of a diagnosis of tuberculosis.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Disclaimer. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention.

Financial support. This work was funded by the National Institute for Communicable Diseases of the National Health Laboratory Service and supported in part by funds from the US Centers for Disease Control and Prevention (Atlanta, GA) Preparedness and Response to Avian and Pandemic Influenza in South Africa (Cooperative Agreement Number U51/IP000155-04).

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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